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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY AND LARDNER LLP SUITE 500 3000 K STREET NW WASHINGTON, DC 20007			EXAMINER SHEN, WU CHENG WINSTON	
			ART UNIT 1632	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/788,410

Applicant(s)

MARTUZA ET AL.

Examiner

Wu-Cheng Winston Shen

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16-20 and 28-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16-20 and 28-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's After-Final amendment filed on 01/08/2007 has been received and entered. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of office action mailed on 10/18/2007 is *withdrawn*.

Claims 1-15 and 21-27 are cancelled. Claims 30-32 are newly added. Claims 16-20 and 28-32 are pending. Claims 16-20 and 28-32 are currently under examination.

This application is a DIV of 09/625,509, filed on 07/25/2000, now PAT 6,699,468, which is a DIV of 09/004,511, filed on 01/08/1998, now PAT 6,139,834, which is a **CON** of 08/478,800, filed on 06/07/1995 ABN, which is a **CON** of 08/264,581, filed on 06/23/1994, now PAT 5,585,096 (changes are in bold for emphasis). The series of parent applications of instant application listed above is based on the Application Data Sheet filed on 08/06/2007.

Claim Objections

1. Previous objection of claims 25-27 (lower claim number) for depending from claim 28 (higher claim number), is *withdrawn* because claims 25-27 have been cancelled. Claims 30-32 are newly added, which correspond to the canceled claims 25-27.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Previous rejection of claims 16-18 and 29 under 35 U.S.C. 102(b) as being anticipated by Chou et al. (Chou et al., Mapping of herpes simplex virus-1 neurovirulence to γ_1 34.5, a gene nonessential for growth in culture. *Science* 250(4985): 1262-6, 1990), is *withdrawn* because the claims have been amended.

Claim 16 is amended to add further limitation "wherein said protein is a cytokine". Chou et al. does not teach this limitation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR

3.73(b).

3. Previous provisional rejection of claims 16-29 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-18 of copending Application No. 10/748,233 is *withdrawn* because Applicant has filed terminal disclaimer on 01/08/2008 and the terminal disclaimer has been approved on 01/23/2008.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 16 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "an alteration in the γ 34.5 gene, wherein said protein is a cytokine". Claim 20 recites "said herpes simplex virus is G207". It is noted that in the art G207 is the name of a specific HSV that contains deletions of both copies of the γ 34.5 gene as well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR). However, the name G207 does not encompass a cytokine in the HSV vector as required by claim 16. Thus, the virus that meets the limitation of being HSV G207 as recited by claim 20 does not meet the limitations of the parent claim 16 requiring a nucleotide sequence encoding a cytokine. It is unclear what exactly "G207" reads on as claimed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 16-20 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein and (ii) an alteration in the γ 34.5 gene such that no functional γ 34.5 gene product is made, wherein said desired protein is a cytokine and wherein the neurovirulence of said herpes simplex virus is attenuated, and for said virus further comprising at least one further gene alteration in ribonucleotide reductase (RR) gene such that no functional ribonucleotide reductase is made, **does not** reasonably provide enablement for a herpes simplex virus with a genome comprising 1) any alteration in the γ 34.5 gene and the ribonucleotide reductase gene other than an alteration that results in a lack of function of each gene product, or 2) for a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The basis of this scope of enablement rejection is hinged on (1) the breadth encompassed by the limitation "an alteration in the γ 34.5 gene " recited in claim 16 as the phrase encompasses any alteration, including silent mutations, and (2) the lack of an enabled use for the claimed virus wherein there is no attenuation of neurovirulence as the specification supports a use only for the claimed virus wherein neurovirulence is attenuated *in vivo* use of the herpes simplex viral vector with attenuated neurovirulence as a result of an alteration in the γ 34.5 gene such that no functional γ 34.5 gene product is made

The nature of the instant invention is a herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein and (ii) an alteration in the γ 34.5 gene such that no functional γ 34.5 gene product is made, wherein said desired protein is a cytokine, wherein the neurovirulence of said herpes simplex virus is attenuated.

The breadth of the claim 16 reads on any alteration in the $\gamma 34.5$ gene, including, for instance, a silent or other mutation in the $\gamma 34.5$ gene at nucleotide level that does not result in a total lack of functional gene products.

The specification discloses the following information relevant to a herpes simplex virus with a genome comprises an alteration in the in the $\gamma 34.5$ gene, in the context of either presence or absence of a null mutation of ICP6 (ribonucleotide reductase gene):

[0028] **FIG. 1** is a schematic illustration of the construction of a mutant herpes simplex virus containing a 1 kB deletion in both copies of the $\gamma 34.5$ gene and an insertion in the ICP6 gene.

[0034] Viruses of the instant invention are engineered to contain alterations in the expression of at least two specific HSV-1 genes: (1) the $\gamma 34.5$ gene and (2) the ribonucleotide reductase gene. Alterations in this regard include any that disrupt the expression of the product of both of the $\gamma 34.5$ gene and the ribonucleotide reductase gene. The presence of such multiple mutations further reduces the possibility of reversion to wild-type pathogenicity.

[0035] Herpes Simplex Virus Vectors with single alterations in the ribonucleotide reductase or $\gamma 34.5$ gene

[0036] Initial work on the use of attenuated herpes simplex virus vectors for use in anti-tumor therapy employed HSV-1 mutated in one gene allowing the vector to replicate in dividing cells, but not in non-dividing cells. Two such single gene-mutant herpes simplex virus vectors are (1) hrR3, deficient in ribonucleotide reductase, containing an Escherichia coli lacZ gene insertion in the ICP6 gene that encodes the large subunit of RR, [Mineta, T. et al., Gene Therapy 1:S78 (1994) and Mineta et al., J. Neurosurg. 80: 381 (1994)]; and (2)

R3616, which contains mutations in both copies of the γ 34.5 gene. Markert et al., *Neurosurgery* 32: 597 (1993).

[0038] Herpes simplex virus ribonucleotide reductase is required for efficient viral growth in non-dividing cells but not in many dividing cells.

[0042] Herpes simplex virus mutants deficient in only the γ 34.5 gene, such as R3616, are attenuated for neurovirulence, which reduces the possible damage to normal brain cells. Goodman et al., *J. Virol.* 63: 1153 (1989); Chou et al., *Science* 250: 1262 (1990).

The specification does not disclose any alteration in the herpes simplex virus γ 34.5 gene other than mutations that disrupt the function of γ 34.5 gene (also known as ICP34.5 gene) (See Figure 2 of instant application).

In the art, it has been shown that variants ICP34.5 causes neuronvirulence. For instance, **Bower et al.** teach that two intra-strain variants of herpes simplex virus type 1 (HSV-1) were isolated from a newborn with fatal disseminated infection. A small-plaque-producing variant (SP7) was the predominant virus (>99%) in the brain, and a large-plaque-producing variant (LP5) was the predominant virus (>99%) in the lung and gastrointestinal tract. PCR analysis using primers from within the ICP34.5 gene indicated differences for SP7, LP5, and KOS. Sequencing data indicated two sets of deletions in the UL34.5 gene that distinguish SP7 from LP5. Both SP7 and LP5 variants were neurovirulent (lethal following intracranial inoculation of young BALB/c mice) (See abstract, and Figures 7 and 8, pages 3848 and 3849, Bower et al. Intra-strain variants of herpes simplex virus type 1 isolated from a neonate with fatal disseminated infection differ in the ICP34.5 gene, glycoprotein processing, and neuroinvasiveness, *J Virol.* 73(5):3843-53, 1999).

With regard to alteration in HSV ribonucleotide reductase gene (claims 18-20 of instant application), **Salvucci et al.** reported polymorphism within the herpes simplex virus (HSV) ribonucleotide reductase large subunit (ICP6) and the viruses harboring the variant ICP6 gene can infect and grow in non-tumor cells, including fibroblasts (See abstract, and Figure 6, page 1128, Salvucci et al., Polymorphism within the herpes simplex virus (HSV) ribonucleotide reductase large subunit (ICP6) confers type specificity for recognition by HSV type 1-specific cytotoxic T lymphocytes, *J Virol.* 69(2):1122-31, 1995).

Therefore, the status of art indicates lack of predictability in terms of (i) whether any alteration other than a null mutation in γ 34.5 will attenuate neurovirulence of a herpes simplex virus, (ii) whether any alteration other than a null mutation in ribonucleotide reductase will render the virus to selectively infect and replicate in fast dividing tumor cells, but not in non-dividing cells. It is worth noting again that the breadth of the claim 1 reads on any alteration in the γ 34.5 gene and the ribonucleotide reductase gene, including a silent mutation in the γ 34.5 gene and the ribonucleotide reductase gene at nucleotide level that does not affect expression of functional gene products as well as mutations that merely alter or reduce activity of the gene products.

Regarding a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence and the effect of having the ability to replicate in dividing cells and not in non-dividing cells, being considered not enabled, the Examiner notes that it is unpredictable what activity the virus will have with anything other than a total lack of function of the two genes. One of skill in the art would not know how to *use* the claimed virus exhibiting any effect of altering the two genes other than the neurovirulence of said herpes simplex virus is attenuated

and said herpes simplex virus and is capable of replication in dividing cells, but not in non-dividing cells. It is worth emphasizing that the full breadth of “alteration” recited in the claim reads on any change in each one of the γ 34.5 gene and the ribonucleotide reductase gene.

Relevant to this unpredictability issue in terms of connection between a genetic mutation and a resulting phenotype, it is noted, as recently reviewed by **Parmley et al.**, 2007, that even silent SNPs encoding the same amino acid residues are not necessarily neutral with regard to their effects on the functions of polypeptides, and there are two additional mechanisms affecting the function of a given polypeptide: (1) modification of protein structure and activity, mediated by induction of translational pausing during co-translational protein folding, and (2) modification of protein abundance mediated by alteration in mRNA stability via changed secondary structures of mRNA, which in turn leads to perturbation in protein synthesis (See abstract, Parmley et al., How do synonymous mutations affect fitness? *Bioessays*, 29(6): 515-9, 2007). In other words, alterations in either protein folding or translational efficiency result on changed protein functions encoded by synonymous mutations.

It is noted that the specification discloses LacZ is used to disrupt ICP34.5 gene (i.e. γ 34.5 gene) (See Figure 1), and the specification also discloses a HSV contains an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein capable of eliciting an immune response in the subject (See paragraph [0024]). The specification discloses that the mutant herpes simplex virus vector of the invention can be further altered to express cytokines, the newly added limitation of claim 16, in the tumor target cell in order to elicit an immune response against the tumor cells. For example, a mutant herpes simplex virus vector can induce viral-mediated killing of tumor cells, which then is amplified by a cytokine-enhanced immune

response, a cytokine having been expressed by the vector itself (See paragraph [0077]).

However, the specification does not provide any support that the expression of LacZ, which was inserted to disrupt ICP34.5 gene, would elicit an immune response in the subject.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 16-20 and 28-32.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 16, 17, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Roizman et al. teaches the following: (i) Novel modified HSV vectors for gene therapy (See abstract, Roizman et al., 2001), which reads on the limitation “an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein” recited in claim 16 of instant applicant application, (ii) The function of the gene g34.5 in its ability to enable the virus to

replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the CNS and eyes and therefore are non-pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001), (iii) The use of the HSV-1 virus with a null mutation in the g34.5 gene provides a method of therapeutic treatment of tumorigenic diseases both in the CNS and in all other parts of the body. The " γ 34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the γ 34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001). Roizman et al. further teaches that the γ 34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001), and (iv) The embodiment of the present invention describes a method which involves combining ICP34.5 (i.e. γ 34.5) or a biological functional equivalent thereof with a pharmaceutically acceptable carrier in order to form a pharmaceutical composition, which reads on claim 29 of instant application.

However, Roizman et al., do not teach do not teach a herpes simplex virus with a genome that expresses an exogenous cytokine gene recited in claim 16, in the context of cancer development and treatment as required by claim 28.

At the time of filing of instant application, transduction of tumor cells *in vitro* with cDNAs encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned *in vivo* to syngeneic animals. For instance, Vile et al. teaches using the 5' flanking region of the murine tyrosinase gene to direct expression of three different cytokine genes [murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF)] specifically to murine melanoma cells (See abstract, Vile et al. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to use the herpes simplex virus vector with disrupted both γ 34.5 that exhibits no neurovirulence, by the teachings of Roizman et al., 2001, and exogenously express a cytokine gene from the HSV vector for treatment of cancer, by the teachings of Vile et al., 1994.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001 on a HSV vector for cancer treatment and the exogenous expression of cytokine in treating melanoma cancer, to arrive at the claimed herpes simplex viruses recited in claims 16, 17, 28, and 29 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, by the teachings of Roizman 2001, to introduce an exogenous cytokine gene into a tumor cell, by the teachings of Vile et al., 1994 because the HSV vector is non-pathogenic, and the exogenous expression of a cytokine gene results in diminishing or eliminating tumorigenicity. One of skill in the art would have been motivated to exogenously express a cytokine gene from the HSV vector with null mutation in

γ 34.5 gene for treatment of cancer because the γ 34.5 gene mutation in the HSV vector would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), and expression of a cytokine diminish or eliminate tumorigenicity, as taught by Vile et al., 1994.

There would have been a reasonable expectation of success given (1) the characteristics of an HSV vector by the combined teachings of Roizman et al. being non-pathogenic, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claims 16, and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claims 16, 17, 28, and 29 above, and further in view of Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991).

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 17, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 taken with Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene (recited in claim 19 of instant application).

At the time of filing of instant application, a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene was known in the art. For instance, Chang et al. teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial lacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir, hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of a foreign gene into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine (i) the characteristics of a mutant herpes simplex virus comprising an nucleotide sequence encoding a cytokine, a disrupted γ 34.5 herpes simplex, which

is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, as taught by combined teachings of Roizman et al. 2001 and Vile et al., 1994, with (ii) the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, as taught by Chang et al. 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001, and Vile et al., 1994, with the teachings of Chang et al. 1991, to arrive at the claimed herpes simplex viruses as recited in claims 16 and 18-20 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. 2001, Vile et al., 1994, with the teachings of Chang et al. 1991 because the disrupted $\gamma 34.5$ gene renders the HSV vector non-pathogenic and the disrupted ribonucleotide reductase gene render the HSV vector specific targeting to fast dividing tumor cells without harming healthy cells, for the treatment of CNS or non-CNS cancers. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, column 5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6 Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the demonstration that the " $\gamma 34.5$ minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific

promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, and (3) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

8. Claim 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994) as applied to claim 16, 17, 28, and 29 above, and further in view of McKay et al. (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and Wright, Jr. (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994).

The teachings of Roizman et al. and Vile et al. have been discussed in the preceding rejection of claims 16, 17, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 taken with Vile et al., 1994.

However, the combined teachings of Roizman et al. and Vile et al., do not teach a herpes simplex virus with a genome that expresses a exogenous cytokine gene, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor

(bFGF) promoter, or epidermal growth factor (EGF) promoter, as recited in claims 30-32 of instant application.

At the time of filing of instant application, it was known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, 1997 teaches the expression of bFGF, EGF can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH) (See title and lines 30-36. column 2, Wright et al., 1997). Furthermore, as indicated before, Roizman et al. further teaches that the γ 34.5 gene placed under a suitable target specific promoter in the context of treating a tumor cell (which reads on claim 28 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001). Accordingly, it would have been *prima facie* obvious the nestin promoter, bFGF promoter, EGF promoter are tumor cell specific promoters, and thereby can be used for expressing an essential viral gene as recited in claims 30-32 of instant application by the combined teachings of Roizman et al., 2001, McKay et al., 1991, and Wright, 1997.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a nucleotide sequences encoding a cytokine, whose transduction of tumor cells with cDNAs encoding various cytokines has been shown to

diminish or eliminate tumorigenicity in syngeneic animals, in a γ 34.5 defective HSV vector, as taught by the combined teachings of Roizman et al., 2001 and Vile et al., 1994, and to have an essential viral gene product under the control of a tumor cell-specific promoter of nestin or bFGF, or EGF, as taught by the teachings of Wright or McKay et al., in the said herpes simplex virus vector with disrupted both γ 34.5 and expressing nucleotide sequences encoding a cytokine, to ensure that the said HSV vector exhibits no neurovirulence and specifically infecting the fast dividing cancer cells in the cancer cells, by the combined teachings of Roizman et al., 2001, Vile 1994, and Chang et al., 1991.

It would have been obvious at the time of filing to combine (i) the teachings of Roizman et al. 2001, and Vile et al., 1994, regarding a HSV vector for cancer treatment with the expression of a nucleotide sequences encoding a cytokine from a HSV vector, wherein as essential viral gene product placed under a suitable target specific promoter, with (ii) the teachings by Wright or McKay et al., regarding gene product being under the control of the tumor specific promoters of nestin or bFGF, or EGF to arrive at the claimed herpes simplex viruses as recited in claims 30-32 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, expresses nucleotide sequence encoding a cytokine, and infects specifically to tumor cells, by combined teachings of Roizman 2001, Vile et al., 1994, and Chang 1999, to introduce the expression of a nucleotide sequences encoding a cytokine for gene therapy, and said HSV vector comprises an essential gene product under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., because the HSV vector being non-pathogenic and specifically infect tumor cells

without harming healthy cells, and the exogenous nucleotide sequence encoding cytokine is expressed only in the tumor cells, as an essential viral gene product is expressed in a tumor specific manner.

There would have been a reasonable expectation of success given (1) the characteristics of an HSV vector by the combined teachings of Roizman et al. and Chang et al. being non-pathogenic and specifically targeting to fast dividing tumor cells, (2) the demonstration of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994, (3) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

9. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-

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3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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